On page 9, please amend the paragraph beginning on line 4 as follows:

This Application is a divisional of U.S. Serial No. 09/442,717, filed November 18, 1999, now allowed, which is a continuation of U.S. Serial No. 08/930,721, filed March 10, 1998, now abandoned, which is a national stage of PCT Application No. US96/04806, filed April 5, 1996, now abandoned, the contents of each of which are hereby incorporated by reference. Throughout this application various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application.

On page 9, please amend the paragraph starting on line 18 as follows:

FIGURE 4A-4F - Nucleic acid and deduced amino acid (single letter code) sequences of human TIE-2 ligand 1 from clone λgt10 encoding htie-2 ligand 1 (SEQ ID NO:1 and SEQ ID NO:2).

On page 9, please amend the paragraph starting on line 22 as follows:

FIGURE 5A-5F - Nucleic acid and deduced amino acid (single letter code) sequences of human TIE-2 ligand 2 ligand 1 from T98G clone (SEQ ID NO:3 and SEQ ID NO:4).

On page 9, please amend the paragraph starting on line 26 as follows:

FIGURE 6A-6F - Nucleic acid and deduced amino acid (single letter code) sequences of human TIE-2 ligand 2 from clone pBluescript KS encoding human TIE 2 ligand 2 (SEQ ID NO:5 and SEQ ID NO:6).

On page 12, please amend the paragraph starting on line 21 as follows:

As described in greater detail below, applicants have isolated and identified novel ligands that bind the TIE-2 receptor. The TIE-2 ligands of the present invention, which may be purified from nature, or made recombinantly, are referred to herein as TIE-2 ligand 1 (or TL1) and TIE-2 ligand 2 (or TL2). TIE-2 ligand 1, which has an amino acid sequence which is encoded, *inter alia*, by the nucleic acid set forth in Figure 4A-4F (SEQ ID NO:1) or Figure 5A-5F (SEQ ID NO:3), is a TIE-2 receptor agonist. TIE-2 ligand 2, which has an amino acid sequence which is encoded, *inter alia*, by the nucleic acid described in Figure 6A-6F (SEQ ID NO:5), is a TIE-2 receptor antagonist.

On page 15, please amend the paragraph starting on line 6 as follows:

Accordingly, the present invention encompasses an isolated and purified nucleic acid molecule comprising a nucleic acid sequence encoding a human TIE-2 ligand, wherein the nucleic acid sequence is selected from the group consisting of:

(a) the nucleic acid sequence comprising the coding region of the human TIE-2 ligand as set forth in Figure 4A-4F (SEQ ID NO:1), Figure 5A-5F (SEQ ID NO:3) or Figure 6A-6F (SEQ ID NO:5);

(b) a nucleic acid sequence that hybridizes under moderately stringent conditions to the nucleic acid sequence of (a) and which encodes a TIE-2 ligand that binds TIE-2 receptor; and

(c) a nucleic acid sequence that is degenerate as a result of the genetic code to a nucleic acid sequence of (a) or (b), and which encodes a TIE-2 ligand that binds TIE-2 receptor.

On page 30, please amend the paragraph starting on line 16 as follows:

In addition, the invention further contemplates compositions wherein the TIE-2 ligand is the receptor binding domains of the TIE-2 ligands described herein. For example, TIE-2 ligand 1 consists of a "coiled coil" domain (beginning at the 5' end and extending to the nucleotide at about position 1160 of Figure 4A-4F (SEQ ID NO:1) and about position 1157 of Figure 5A-5F (SEQ ID NO:3)) and a fibrinogen-like domain (which is encoded by the nucleotide sequence of Figure 4A-4F (SEQ ID NO:1) beginning at about position 1161 and about position 1158 of Figure 5A-5F (SEQ ID NO:3)). The fibrinogen-like domain of TIE-2 ligand 2 is believed to begin on or around the same amino acid sequence as in ligand 1 (FRDCA) which is encoded by nucleotides beginning around 1197 of Figure 6A-6F (SEQ ID NO:5). Multimerization of the coiled coil domains during production of the ligand hampers purification. As described in Example 19, Applicants have discovered, however, that the fibrinogen-like domain comprises the TIE-2 receptor binding domain. The monomeric forms of the fibrinogen-like domain do not, however, appear to bind the receptor. Studies utilizing myc-tagged fibrinogen-like domain, which has been "clustered" using anti myc antibodies, do bind the TIE-2 receptor. [Methods of production of "clustered ligands and ligandbodies are described in Davis, et al. Science 266:816-819 (1994)]. Based on these finding, applicants produced "ligandbodies" which comprise the fibrinogen-like domain of the TIE-2 ligands coupled to the Fc domain of IgG ("fFc's"). These ligandbodies, which form dimers, efficiently bind the TIE-2 receptor. Accordingly, the present invention contemplates the production of TIE-2 ligandbodies which

may be used as targeting agents, in diagnostics or in therapeutic applications, such as targeting agents for tumors and/or associated vasculature wherein a TIE-2 antagonist is indicated.

On page 51, please amend the paragraph starting on line 1 as follows:

The coding region from the clone λgt10 encoding htie-2 ligand 1 was sequenced using the ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). The nucleotide and deduced amino acid sequence of human TIE-2 ligand from the clone λgt10 encoding htie-2 ligand 1 is shown in Figure 4A-4F (SEQ ID NO:1 and SEQ ID NO:2).

On Page 51, please amend the paragraph starting on line 7 as follows:

In addition, full length human tie-2 ligand cDNA clones were obtained by screening a human glioblastoma T98G cDNA library in the pJFE14 vector. Clones encoding human TIE-2 ligand were identified by DNA hybridization using a 2.2 kb XhoI fragment from the deposited tie-2 ligand clone (ATCC NO. 75910) as a probe (see Example 6 above). The coding region was sequenced using the ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). This sequence was nearly identical to that of clone λgt10 encoding htie-2 ligand 1. As shown in Figure 4A-4F (SEQ ID NO:1), the clone λgt10 encoding htie-2 ligand 1 contains an additional glycine residue which is encoded by nucleotides 1114-1116. The coding sequence of the T98G clone does not contain this glycine residue but otherwise is identical to the coding sequence of the clone λgt10 encoding htie-2 ligand 1. Figure 5A-5F (SEQ ID NO:3 and SEQ ID NO:4) sets forth the nucleotide and deduced amino acid sequence of human TIE-2 ligand from the T98G clone.

On page 51, please amend the paragraph starting on line 26 as follows:

A human fetal lung cDNA library in lambda gt-10 (see Figure 3) was obtained from Clontech Laboratories, Inc. (Palo Alto, CA). Plaques were plated at a density of 1.25 x 10^6/20x20 cm plate, and replica filters taken following standard procedures (Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., page 8.46, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). Duplicate filters were screened at low stringency (2 x SSC, 55° C) with probes made to the human TIE-2 ligand 1 sequence. One of the duplicate filters was probed with a 5' probe, encoding amino acids 25 - 265 of human TIE-2 ligand 1 as set forth in Figure 4A-4F (SEQ ID NO:2). The second duplicate filter was probed with a 3' probe, encoding

amino acids 282 - 498 of human TIE-2 ligand 1 sequence (see Figure 4A-4F (SEQ ID NO:2)). Both probes were hybridized at 55° C in hybridization solution containing 0.5 mg/ml salmon sperm DNA. Filters were washed in 2 x SSC at 55° C and exposed overnight to X-ray film. In addition, duplicate filters were also hybridized at normal stringency (2 x SSC, 65° C) to the full length coding probe of mouse TIE-2 ligand 1 (F3-15, XhoI insert). Three positive clones were picked that fulfilled the following criteria: i. hybridization had not been seen to the full length (mouse) probe at normal stringency, and ii. hybridization was seen at low stringency to both 5' and 3' probes. EcoRI digestion of phage DNA obtained from these clones indicated two independent clones with insert sizes of approximately 2.2kb and approximately 1.8 kb. The 2.2kb EcoRI insert was subcloned into the EcoRI sites of both pBluescript KS (Stratagene) and a mammalian expression vector suitable for use in COS cells. Two orientations were identified for the mammalian expression vector. The 2.2kb insert in pBluescript KS was deposited with the ATCC on December 9, 1994 and designated as pBluescript KS encoding human TIE 2 ligand 2. The start site of the TIE-2 ligand 2 coding sequence is approximately 355 base pairs downstream of the pBluescript EcoRI site.

On page 54, please amend the paragraph starting on line 6 as follows:

The coding region from the clone pBluescript KS encoding human TIE-2 ligand 2 was sequenced using the ABI 373A DNA sequencer and Taq Dideoxy Terminator Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA). The nucleotide and deduced amino acid sequence of human TIE 2 ligand from the clone pBluescript KS encoding human TIE-2 ligand 2 is shown in Figure 6A-6F (SEQ ID NO:5 and SEQ ID NO:6).